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(54) Title: TRANSDERMAL DELIVERY SYSTEM CONTAINING BUPRENORPHINE

(57) Abstract

The present invention relates to a transdermal delivery composition containing buprenorphine and patches containing the same. More particularly, the transdermal delivery composition of the present invention comprising 1 ~ 8 wt.% of buprenorphine or its salts, 20 ~ 60 wt.% of water, 5 ~ 30 wt.% of $C_3$-~$C_4$ alkane diols, 10 ~ 40 wt.% of $C_2$-~ $C_3$ alcohols, 5 ~ 30 wt.% of triacetin and 0.5 ~ 10 wt.% of one or more compounds selected from the group consisting of $C_8$-~$C_{18}$ fatty acids, $C_8$-~$C_{18}$ aliphatic alcohols, esters between $C_2$-~$C_4$ alkanediols and $C_8$-~$C_{18}$ fatty acids, esters between $C_3$-~$C_4$ alkanetriols and $C_8$-~$C_{18}$ fatty acids, esters between $C_1$-~$C_4$ alcohols with $C_8$-~$C_{18}$ fatty acids, and terpenes which, unlike conventional transdermal delivery compositions, enables not only to provide superior transdermal penetration of buprenorphine but also to reduce the effective dosage of fatty acids and esters thereof, that are known to cause serious skin irritation.

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# TRANSDERMAL DELIVERY SYSTEM CONTAINING BUPRENORPHINE

## BACKGROUD OF THE INVENTION

### Field of the Invention

The present invention relates to a transdermal delivery composition containing buprenorphine and patches containing the same and more particularly, to a novel transdermal delivery composition containing buprenorphine and patches therefrom, wherein the composition comprises buprenorphine or its salt; $C_3$-$C_4$ alkanediols; $C_2$-$C_3$ alcohols; triacetin; and one or more compounds selected from the group consisting of $C_8$-$C_{18}$ fatty acids; $C_8$-$C_{18}$ aliphatic alcohols; esters between $C_2$-$C_4$ alkanediols and $C_8$-$C_{18}$ fatty acids; esters between $C_3$-$C_4$ alkanetriols and $C_8$-$C_{18}$ fatty acids; esters between $C_1$-$C_4$ alcohols and $C_8$-$C_{18}$ fatty acids; and terpenes.

### Description of the Related Arts

In general, analgesic agents having a narcotic property become effective when they react with opium receptors which are prevalent in central and peripheral nervous systems. The opium receptors are differentially distributed within the central nervous system and they are classified as μ, κ, σ and δ types according to the difference in *in vivo* pharmacological actions of the narcotic analgesia and the analgesic analogues. The currently used narcotic analgesia usually reacts with μ, κ and σ receptors and they can be also subdivided into an agonist, a partial agonist, and an antagonist.

The target composition in the present invention is buprenorphine of which the chemical name is [5α, 7α (s)]-17-cyclopropylmethyl-α-(1,1-

dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-ethyl-6,14-ethenomorphinan-7-methanol, and buprenorphine hydrochloride which is a salt formed between buprenorphine and HCl. Buprenorphine exhibits an analgesic effect as a partial agonist for μ receptors which are mostly present in supraspinal cord. It can be also used as a detoxicant or a therapeutic agent to treat withdrawal symptoms of drug addicts because it has relatively higher affinities for receptors than other narcotic drugs such as morphine sufficient to serve the role as an agonist. Moreover, its activity can last at least twice longer and the analgesic effect is also 50-100 times greater than that of morphine.

Buprenorphine has been developed as a commercial product for intravenous(IV) or intramuscular(IM) injections such as Buprenex™ (Morton-Norwich, USA) and Tengesic™ (Reckitt and Coleman, U.S.A.) and used to relieve the acute pains of those patients suffering from trauma, myocardinal infarction, and other serious medical conditions. The recommended dose of administration of the buprenorphine is 0.3 - 0.6 mg per each intravenous or intramuscular injection once in every 6-8 hrs. When orally administered, the drug becomes metabolized by so-called first pass effect in stomach and liver, and the resulting bioavailability reaches only 10 -15% and thus not considered very practical.

The previous types of buprenorphine preparations had drawbacks that they had relatively low patients' adaptability due to the inconveniences in administration and also the low efficiency of the drug absorption by the body; therefore, it was in high demand to develop a transdermal drug delivery system with long-lasting effect (1-3 days/application) and higher absorption efficiency.

In general, the transdermal drug delivery system has the following

advantages. First, unlike oral administration where drugs taken by patients have to go through the gastrointestinal tract and become rendered inactive by digestive enzymes, this system enables to determine the exact dose of each administration by eliminating unpredictable factors. Second, it can help the pharmacological actions of the transdermally delivered drugs last to the level equivalent to that of intravenous injection. Third, the delivering rate of drugs into a body can be easily controlled thus maximizing the effect and also minimizing the side-effects. Fourth, the delivering drug preparations can be easily and instantly removed when the drug being delivered shows a harmful result. Fifth, the way of administration is simpler than injectional method and patients can well adapt to the system comparable to the oral administration. In this type of drug delivery system, the drug penetrates the dermis and exhibits the systemic effect so that the effective blood concentration can be monitored unlike topical preparations which show only topical effects. Notwithstanding the aforementioned advantages of the transdermal drug delivery, there still appear many obstacles in developing new version of transdermal drug delivery because the skin generally works as a strong barrier against most drugs. For example, a given drug shall penetrate keratotic layer, epidermis, dermis and the walls of capillary blood vessels in order to exhibit in the body. In general, the keratotic layer, the outmost layer of human skin is only approximately 10 μm thick, however, it is the most important barrier in skin penetration and thus it is required to change the physicochemical properties of the keratotic layer, lower diffusional resistance by reversible damage or accelerate the distribution of the drug by enhancing the solubility in order to acquire the appropriate penetration rate of a given drug. The materials that meet the above requirements are collectively termed as a skin penetration enhancer. The fact that octanol-water partition coefficient of

buprenorphine is 427 indicates that buprenorphine is rather highly lipophilic and also implies that viable epidermis can work as another barrier in addition to the above keratotic layer during the skin penetration process of the drug. Therefore, the use of enhancers appears essential in transdermal drug delivery and the prior art in this field is delineated hereunder:

European Patent No. 0 432 945 discloses the use of fatty acids or their ester compounds as enhancers for treating cocaine or heroin addictions and European Patent No. 0 282 156 discloses the use of buprenorphine as one example of corticosteroids used to alleviate the skin irritation aroused by drugs. In particular, European Patent No. 0 368 409 discloses the use of polar solvents such as $C_3$-$C_4$ diols and $C_3$-$C_6$ triols as a solvent for buprenorphine and fatty alcohols, fatty acids and fatty acid esters as transdermal penetration enhancers.

U. S. Patent No. 5,069,909 discloses the combinatorial skin penetration enhancers which uses propylene glycol monolaurate and capric acid or oleic acid added to water-soluble acrylic pressure sensitive adhesives and U. S. Patent No. 5,229,130 discloses vegetable oils such as soybean oil, palm oil as an enhancer for narcotic analgesia. U. S. Patent No. 4,879,297 describes water-soluble suspensions of both saturated and unsaturated fatty acids and their ester compounds that can not only alleviate the skin irritation aroused by skin penetrating enhancers but also increase the skin penetration rate compared to systems using organic solvents. U. S. Patent No. 5,601,839 describes that triacetin can be also used as a skin penetration enhancer as well as a solubilizer for basic drugs containing buprenorphine with their pKa's greater than 8.0. The conventional transdermal drug delivery preparations generally had a few negative aspects such as having an unsatisfactory skin penetration rate and containing a fairly large amount of fatty acids or their ester compounds that resulted in serious skin irritation, and thus transdermal delivery composition

containing buprenorphine that can overcome with the above-mentioned problems is in urgent request.

## SUMMARY OF THE INVENTION

In view of the above considerations, the inventors herein have intensively studied to solve the above-mentioned problems. As a result, the inventors realized that an appropriate combination of hydrophilic skin penetration enhancers and hydrophobic skin penetration enhancers provides excellent skin penetration rates and reduces the effective dosage of fatty acids or their esters that resulted in serious skin irritation.

The object of the present invention is to provide a transdermal delivery composition containing buprenorphine and the further object of the invention is to provide patches containing the same.

## Detailed Description of the Invention

The present invention relates to the transdermal delivery composition comprising 1 ~ 8 wt. % of buprenorphine or its salts, 20 ~ 60 wt. % of water, 5 ~ 30 wt. % of $C_3$ ~ $C_4$ alkanediols, 10 ~ 40 wt. % of $C_2$ ~ $C_3$ alcohols, 5 ~ 30 wt. % of triacetin and 0.5 ~ 10 wt. % of one or more compounds selected from the group consisting of $C_8$ ~ $C_{18}$ fatty acids, $C_8$ ~ $C_{18}$ aliphatic alcohols, esters between $C_2$ ~ $C_4$ alkane diols and $C_8$ ~ $C_{18}$ fatty acids, esters between $C_3$ ~ $C_4$ alkanetriols and $C_8$ ~ $C_{18}$ fatty acids, esters between $C_1$ ~ $C_4$ alcohols and $C_8$ ~ $C_{18}$ fatty acids, and terpenes which, unlike conventional transdermally delivered drug compositions, enables not only to provide superior transdermal penetration of buprenorphine but also to reduce the effective dosage of fatty acids and esters thereof, that are known to cause serious skin irritation.

The present invention can be described in more detail as follows.

The buprenorphine in the present invention refers to both the unionized type of buprenorphine and its salts, and the preferred concentration of the buprenorphine in the transdermal delivery composition is approximately 1-10 wt. % considering the solubility of the buprenorphine (16 mg/mL at 32 ℃ in distilled water; 22.5 mg/mL at 32 ℃ in propylene glycol). If the content of buprenorphine is less than 1 % by weight, the effective concentration in blood stream cannot be achieved using the patch of the present invention, while if it is more than 10 % by weight, the buprenorphine becomes unstable and subsequently precipitated as a crystal because it exceeds the solubility limit in the given transdermal delivery composition of the present invention.

Examples of $C_3$ ~ $C_4$ alkanetriols that can be used as a solvent of transdermal composition in this invention include propylene glycol, 1,3-propandiol, 1,2-butandiol, 1,3-butandiol, 1,4-butandiol, with its wt.% ranges from 5 to 30, respectively. Among these, propylene glycol is the most preferred. Propylene glycol is a hydrophilic solvent, because it can work excellently both for hydrophilic and lipophilic drugs, serve as an effective auxiliary solvent for other tansdermal penetration enhancers (fatty acids, fatty alcohols, their ester compounds, terpene compounds, etc.), and keep the thermodynamic activity at an elevated level. If the content of $C_3$ ~ $C_4$ alkanetriols is less than 5 wt.%, the amount of transdermal skin penetration of drugs is much reduced because uniform composition cannot be formed due to the lack in compatibility between water and other lipophilic transdermal penetration enhancers. If it is more than 30 wt.%, it would result in the decrease of contents of other transdermal penetration enhancers and subsequently reduce the amount of transdermal skin penetration of drugs.

The preferred examples of the above-mentioned $C_2$ ~ $C_3$ alcohols are ethanol, propyl alcohol and isopropyl alcohol and the preferred amount used is

10-40 wt.%. Among the above examples, ethanol is the most preferred because it reversibly changes the structure of the keratotic layer by extracting polar lipids therefrom; however, when the ethanol is removed the skin can be recovered to the original state. Here, if the content of $C_2 \sim C_3$ alcohol is below 10 wt.%, the skin penetration rate of drug becomes poor while if the content exceeds 40 wt.% the skin penetration rate of drug does not get enhanced further and the overall penetration become decreased because the amount of other enhancers are decreased.

Triacetin is an effective solvent of buprenorphine as well as an enhancer of transdermal penetration, and the preferred amount of triacetin is 5~30 wt.%. If the amount is less than 5 wt.% the transdermal penetration of drug becomes poor while if it exceeds 30 wt.% there is no additional enhancement of transdermal penetration.

Meanwhile, the above-mentioned three solvents and their combined uses are not sufficient to provide excellent transdermal delivery of drugs, and there must be added other ingredients which can maximize the transdermal penetration with a small amount as follows: i.e., one or more compounds with 0.5~10 wt. % selected from $C_8 \sim C_{18}$ fatty acids, $C_8 \sim C_{18}$ aliphatic alcohols, esters between $C_2 \sim C_4$ alkanediols and $C_8 \sim C_{18}$ fatty acids, esters between $C_3 \sim C_4$ alkanetriols and $C_8 \sim C_{18}$ fatty acids, esters between $C_1 \sim C_4$ alcohols and $C_8 \sim C_{18}$ fatty acids, and terpenes. The above-mentioned compounds can disrupt the bilayer structure of the keratotic layer to enhance intercellular fluidity, thereby enhancing the skin penetration rate of drugs when they are used in combination with propylene glycol and ethanol. Here, if the content of a given compound is less than 0.5 wt.% then the penetration becomes poor while it generates various kinds of dermatitis such as erythema, edema, crust, etc. if it exceeds 10 wt.%.

Examples of the above $C_8 \sim C_{18}$ fatty acids include capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

Examples of the above $C_8 \sim C_{18}$ aliphatic alcohols include octanol, nonanol, decanol, lauryl alcohol and oleyl alcohol.

Examples of the above esters between $C_2 \sim C_4$ alkanediols and $C_8 \sim C_{18}$ fatty acids include ethylene glycol monolaurate, propylene glycol monolaurate, propylene glycol dilaurate, and the mixture between propylene glycol monolaurate and propylene glycol dilaurate (Gattefosse, lauroglycol FCC).

Examples of the above esters between $C_3 \sim C_4$ alkanetriols and $C_8 \sim C_{18}$ fatty acids include glycerol monooleate, glycerol dioleate, glycerol trioleate, glycerol monolaurate, glycerol dilaurate, glycerol trilaurate, glycerol tricaprylrate, glycerol tricaprate and their mixtures.

Examples of the above esters between $C_1 \sim C_4$ alcohols and $C_8 \sim C_{18}$ fatty acids include methyl laurate, ethyl oleate and isopropyl myristate, and terpenes include L-menthol, menthone, D-limonene, 1,8-cineole, nerolidol, carveol and camphor.

The above-mentioned compounds can be mixed to generate a homogeneous state, and adequate amount of Cremophor RH40 can be added as an emulsifier for microemulsion if the system becomes separated.

The patch that is designed for the stable transdermal delivery of drugs containing buprenorphine in the present invention can be manufactured in a matrix patch or in a reservoir patch, and preferably a matrix patch. The matrix patch can be manufactured in a single layered or multi-layered solid form or in a hydrogel form, and of the matrix types the hydrogel form is most suitable to stably keep the transdermal delivery composition in the patch.

The above hydrogel as a matrix comprises 60~85 wt. % of transdermal delivery composition, 1~10 wt. % of hydroxyethyl cellulose, 3~20 wt. % of polyvinyl pyrrolidone and 5~20 wt. % of polyvinyl alcohol. Here, the patch is first coated with an adhesive and then deposited with hydrogel and finally covered with a removable cover.

The following examples illustrate various aspects of the present invention herein but are not to be construed to limit claims in any manner.

**Examples 1-14**

All the mixtures listed in Table 1 were dissolved by adding 2 wt. % of buprenorphine, respectively, and there were also added adequate amount of Cremophor RH40 additionally for emusification when a homogeneous system was not generated, and the transdermal delivery composition containing buprenorphine was finally produced.

**Table 1.**

| Examples | Transdermal delivery compositions and their Contents (wt. %) |
|---|---|
| Example 1 | water/propylene glycol/triacetin/ethanol/lauryl alcohol (30/30/15/20/5) |
| Example 2 | water/propylene glycol/triacetin/ethanol/ propylene glycol monolaurate (32/30/15/22/1) |
| Example 3 | water/ propylene glycol/ triacetin/ ethanol/ lauroglycol FCC/ Cremophor (30/30/15/20/5/4.7) |
| Example 4 | water/propylene glycol/triacetin/ethanol/methyl laurate/ Cremophor (30/30/15/20/5/6.2) |
| Example 5 | water/propylene glycol/triacetin/ethanol/oleyl alcohol/ Cremophor (47/20/10/20/5/4) |
| Example 6 | water /propylene glycol/ triacetin/ ethanol/ nonanol/ Cremophor (32/30/15/20/3/1.7) |
| Example 7 | water /propylene glycol/ triacetin/ ethanol/ limonene/ Cremophor (40/20/10/20/10/11.8) |
| Example 8 | water/propylene glycol/triacetin/ethanol/glycerine monolaurate/nonanol/Cremophor (40/17/7/30/5/1/1.7) |
| Example 9 | water/propylene glycol/triacetin/ethanol/methyl laurate/ nonanol/ Cremophor (40/17/7/30/5/1/6) |
| Example 10 | water/propylene glycol/triacetin/ethanol/lauryl alcohol/ nonanol/ Cremophor (40/19/9/30/1/1/1.9) |
| Example 11 | water/propylene glycol/triacetin/ethanol/lauryl alcohol/ nonanol/ Cremophor (40/18/8/30/2/2/1.7) |
| Example 12 | water /propylene glycol/ triacetin/ ethanol/ oleyl alcohol /nonanol/ Cremophor (40/18/8/30/3/1/5.2) |
| Example 13 | water/propylene glycol/triacetin/ethanol/nonanol/ limonene/ Cremophor (42/20/10/20/3/5/8) |
| Example 14 | water/propylene glycol/triacetin/ethanol/ propylene glycol monolaurate/ nonanol/ Cremophor (40/18/8/30/1/1/1.5) |

**Comparative Examples 1-26**

All the mixtures listed in Table 2a and 2b were dissolved by adding 2 wt. % of buprenorphine, respectively. When the systems obtained were not

homogeneous there were added adequate amount of Cremophor RH40 additionally for emusification, and finally the transdermal delivery composition containing buprenorphine was produced.

**Table 2a.**

| Comp. examples | Transdermal delivery composition and their Contents (wt.%) |
|---|---|
| Comp. example 1 | water/ ethanol (60/40) |
| Comp. example 2 | water/propylene glycol/ ethanol (50/30/20) |
| Comp. example 3 | water/propylene glycol/ ethanol (30/50/20) |
| Comp. example 4 | Water/triacetin/ethanol (40/40/20) |
| Comp. example 5 | water/propylene glycol/triacetin/ethanol (33/30/15/22) |
| Comp. example 6 | water/propylene glycol/ethanol/oleylalcohol/ Cremophor (30/45/20/5/7.3) |
| Comp. example 7 | water/triacetin/ethanol/ lauryl alcohol (30/45/20/5) |
| Comp. example 8 | water/propylene glycol/ lauryl alcohol (5/80/15) |
| Comp. example 9 | water/propylene glycol/ ethanol/ lauryl alcohol / Cremophor (40/35/20/5/6.2) |
| Comp. example 10 | water/propylene glycol/ethanol/lauryl alcohol/ Cremophor (30/45/20/5/3) |
| Comp. example 11 | water/propylene glycol/ propylene glycol monolaurate /lauryl alcohol (5/80/10/5) |
| Comp. example 12 | water/ propylene glycol/ ethanol /nonanol (32/45/20/3) |
| Comp. example 13 | propylene glycol/ethanol/propylene glycol monolaurate (5/80/15) |

**Table 2a** (continued)

| Comp. examples | Transdermal Delivery Composition and their Contents (wt.%) |
|---|---|
| Comp. example 14 | water/ propylene glycol/ ethanol/ propylene glycol monolaurate (30/45/20/5) |
| Comp. example 15 | water/propylene glycol/ ethanol/ lauroglycol FCC/ Cremophor (30/45/20/5/6) |
| Comp. example 16 | water/ propylene glycol/ ethanol/ methyl laurate/ Cremophor (30/45/20/5/6) |
| Comp. example 17 | water/ propylene glycol/ ethanol/ glycerol monolaurate (30/45/20/5) |
| Comp. example 18 | water/ propylene glycol/ ethanol/ menthol/ Cremophor (45/30/20/5/5.3) |
| Comp. example 19 | water/ propylene glycol/ ethanol/ limonene/ Cremophor (45/30/20/5/16.8) |
| Comp. example 20 | water/ propylene glycol/ oleic acid/ Cremophor (50/49/1/5) |
| Comp. example 21 | water/propylene glycol/ ethanol /oleic acid/ Cremophor (30/49/20/1/2.7) |
| Comp. example 22 | water/propylene glycol/ ethanol /linoleic acid/ Cremophor (50/27/20/3/3.0) |
| Comp. example 23 | water/propylene glycol/ triacetin/ethanol /lauryl alcohol (30/50/5/10/5) |
| Comp. example 24 | water/propylene glycol/ triacetin/ethanol /lauryl alcohol (30/10/5/50/5) |
| Comp. example 25 | water/propylene glycol/ triacetin/ethanol /lauryl alcohol (30/15/40/10/5) |
| Comp. example 26 | water/propylene glycol/ triacetin/ethanol /lauryl alcohol (69/5/10/5/1) |

**Experimental Example 1**

The skin penetration rate of a drug containing buprenorphine was determined using a Franz Diffusion Cell (Crown glass Co., USA, Model FDC-400). The Franz Diffusion Cell consists of both a donor and a receptor. The effective area of the skin exposed to the receptor solution was 0.636 $cm^2$ and the amount was 5 mL. 0.1 wt. % of sodium azide in purified water was used as a receptor solution and the solution was continuously stirred at 600 rpm by using a magnetic stirrer while maintaining the temperature at 32±0.5℃ by using a constant-temperature circulation pump. The skin tested was 100~800 μm human cadaver skin which was sliced and kept frozen at -20℃, and was immersed in purified water for 20 min to be thawed right before use. Each cadaver skin was then set out so that the keratin layer of the skin faces the donor and 500 μL of dermal penetration enhancer was added to the donor and finally the donor was sealed to prevent evaporation. Then, 300 μL was taken out from the receptor at fixed time intervals and the same amount was immediately replenished.

Liquid chromatography was performed by using $C_8$ column to separate the buprenorphine contained in the receptor solution taken out as aforementioned, and a mixture between methanol and acetonitrile in a 7:3 ratio was combined with 0.01 M buffered phosphate solution (pH 5.0) in a 85:15 ratio to make a developing solvent. The UV detector was set at 215 nm.

The skin penetration rate of a drug was determined by the amount of the drug penetrated per unit area of the skin per unit time, according to formula 1 and the result is shown in the following Table 3.

[Formula 1]

$$J_s = 1/A(dQ/dt)ss$$

wherein $J_s$ represents the skin penetration rate of a given drug at a steady state, A represents the skin area involved in the above penetration, and (dQ/dt)ss represents the amount of a drug that penetrates skin per unit time at a steady state.

**Table 3**

| Examples | Penetration Rate ($\mu g/cm^2 \cdot hr$) | Comparative Examples | Penetration Rate ($\mu g/cm^2 \cdot hr$) | Comparative Examples | Penetration Rate ($\mu g/cm^2 \cdot hr$) |
|---|---|---|---|---|---|
| Example 1 | 50.9 | Comparative Example 1 | 0.5 | Comparative Example 15 | 13.1 |
| Example 2 | 19.7 | Comparative Example 2 | 0.6 | Comparative Example 16 | 6.4 |
| Example 3 | 24.7 | Comparative Example 3 | 0.3 | Comparative Example 17 | 6.4 |
| Example 4 | 22.8 | Comparative Example 4 | 0.3 | Comparative Example 18 | 8.2 |
| Example 5 | 22.3 | Comparative Example 5 | 0.5 | Comparative Example 19 | 7.6 |
| Example 6 | 40.7 | Comparative Example 6 | 9.0 | Comparative Example 20 | 0.8 |
| Example 7 | 23.4 | Comparative Example 7 | 10.5 | Comparative Example 21 | 2.1 |
| Example 8 | 25.4 | Comparative Example 8 | 7.1 | Comparative Example 22 | 1.7 |
| Example 9 | 20.5 | Comparative Example 9 | 6.3 | Comparative Example 23 | 19.6 |
| Example 10 | 38.3 | Comparative Example 10 | 14.7 | Comparative Example 24 | 12.5 |
| Example 11 | 62.8 | Comparative Example 11 | 5.8 | Comparative Example 25 | 17.0 |
| Example 12 | 22.5 | Comparative Example 12 | 12.0 | Comparative Example 26 | 10.8 |
| Example 13 | 21.6 | Comparative Example 13 | 4.8 | | |
| Example 14 | 42.8 | Comparative Example 14 | 16.9 | | |

The above Table 3 shows that the transdermally delivered drug compositions containing buprenorphine listed in the Examples 1~14 of the present invention are much improved on the average in its rate of skin penetration as compared to those in the Comparative Examples 1~22 which are based on the traditional methods. When comparing the skin penetration rate of compositions between the Examples 1~7 and the Examples 8~14, it is evident that the rates were in general greater in the Examples 8~14 than in the Examples 1~7. Considering that the Examples 1~7 have compositions containing three major ingredients of the present invention, (i.e., propylene glycol, triacetin and ethanol) and only one kind of penetration enhancer while the Examples 8~14 have two kinds of enhancers in addition to the above-mentioned three major ingredients, the above result implies that addition of two or more kinds of enhancers can result in improve the skin penetration rate.

In the above Comparative Examples 1~5, the compositions were either single or combinations of ingredients selected from water, ethanol, propylene glycol and triacetin, and the skin penetration rate was as low as 0.3~0.6 μg /$cm^2$· hr and this also supports the idea that the addition of enhancers in the present invention can generate a synergistic effect.

The compositions listed in Comparative Examples 6~22 are deficient of one or two of the aforementioned major ingredients used in the present invention and also showed lower skin penetration rates as compared to those in the Examples of the present invention, thus implying that the above three major ingredients are essential in transdermally delivered drug compositions.

The compositions listed in Comparative Examples 23~26 show the compositions where one of the compositions listed in Example 1 is used in excess and the fact that the resulting penetration rates of those compositions are much lower than those in the Example 1 indicates that the range of each

ingredient presented in the present invention is quite appropriate.

**Formulation Example 1~2 and Comparative Formulation Example 1~3: Manufacturing of Patches using single-layered hydrogel matrix**

To manufacture a hydrogel matrix, the concentration of buprenorphine was adjusted to 2 % by weight of the total hydrogel matrix and compositions listed in Table 4 prepared so that each composition being exclusive of water and were homogeneously dissolved by adding 6 wt. % of Kollidon 90F ™ (a commercial polypyrrolidone by BASF). Then, 10 wt. % of polyvinyl alcohol, dissolved in adequate amount of distilled water and having 2,500 degree of polymerization, was added to the above mixture and placed under vigorous stirring until the mixture became homogeneous and 3 wt. % of hydroxy ethyl cellulose (MW 240,000) was added to it. The resulting mixture was then molded to have the thickness of 2 mm, placed in a refrigerator for gellation to obtain a hydrogel.

To manufacture patches by using the hydrogel obtained from the above step, films pre-coated with acrylic adhesives were laminated at the size of 10~20 $cm^2$, and 5~10 $cm^2$ of non-permeable films were placed on top of them to prevent the penetration of transdermally delivered drug containing buprenorphine. The hydrogels were then cut out at the same size of the non-permeable films and placed on top of them and were finally covered with fluoride compound to produce the desired patches.

**Table 4**

| Classification | Composition of Hydrogel and the mixed ratio (wt.%) |
|---|---|
| Formulation 1 | water/propylene glycol/ triacetin/ethanol /lauryl alcohol/ hydroxyethyl cellulose/ polyvinyl pyrrolidone/polyvinyl alcohol (22/22/11/15/4/2/4/4) |
| Formulation 2 | water/propylene glycol/ triacetin/ethanol /lauryl alcohol/Kollicoat MAE 30D®/ hydroxyethyl cellulose/ polyvinyl pyrrolidone/ polyvinyl alcohol (29/20/10/14/0.7/4/5/12/5) |
| Comparative Formulation 1 | water/propylene glycol/ propylene glycol monolaurate/ Cremophor /hydroxyethyl cellulose/ polyvinyl pyrrolidone/ polyvinyl alcohol (57/21/4/1/4/8/4) |
| Comparative Formulation 2 | water/propylene glycol/ propylene glycol monolaurate/ ethanol /hydroxyethyl cellulose/ polyvinyl pyrrolidone/ polyvinyl alcohol (32/33/4/15/4/8/4) |
| Comparative Formulation 3 | water/propylene glycol/ lauroglycol/ethanol/ Cremophor /hydroxyethyl cellulose/ polyvinyl pyrrolidine/ polyvinyl alcohol (29/25/6/19/6/4/8/4) |

**Experimental Example 2**

The skin penetration rates of the hydrogels produced in the Formulation Examples and Comparative Examples were measured using the same method as described in the above Experimental Example 1. Here each hydrogel was prepared to have an area of 0.636 $cm^2$ and was set out so that it could closely contact with keratin layer of human cadaver skin, and the result is shown in Table 5.

**Table 5**

| Classification | Penetration Rate ($\mu g/cm^2 \cdot hr$) | Classification | Penetration Rate ($\mu g/cm^2 \cdot hr$) |
|---|---|---|---|
| Formulation 1 | 8.1 | Comparative Formulation 1 | 2.3 |
| Formulation 2 | 4.9 | Comparative Formulation 2 | 1.3 |
| | | Comparative Formulation 3 | 0.9 |

As shown in the above Table 5, the compositions which contain additional ingredient such as lauryl alcohol in addition to the three major ingredients of propylene glycol, ethanol, and triacetin in the present invention are shown to be more effective in improving the skin penetration rate of the drugs.

# CLAIMS

**What is claimed is:**

1. A transdermal delivery composition comprising 1~8 wt. % of buprenorphine or its salts, 20~60 wt. % of water, 5~30 wt. % of $C_3$~$C_4$ alkanediols, 10~40 wt. % of $C_2$~$C_3$ alcohols, 5~30 wt. % of triacetin and 0.5~10 wt. % of one or more compounds selected from the group consisting of $C_8$~$C_{18}$ fatty acids, $C_8$~$C_{18}$ aliphatic alcohols, esters between $C_2$~$C_4$ alkanediols and $C_8$~$C_{18}$ fatty acids, esters between $C_3$~$C_4$ alkanetriols and $C_8$~$C_{18}$ fatty acids, esters between $C_1$~$C_4$ alcohols and $C_8$~$C_{18}$ fatty acids, and terpenes.

2. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein $C_3$ ~ $C_4$ alkanetriols are selected from the group consisting of propylene glycol, 1,3-propandiol, 1,2-butandiol, 1,3-butandiol, and 1,4-butandiol.

3. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein $C_2$ ~ $C_3$ alcohols are selected from the group consisting of ethanol, propyl alcohol and isopropyl alcohol.

4. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein $C_8$ ~ $C_{18}$ fatty acids are selected from the group consisting of capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid.

5. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein $C_8$ ~ $C_{18}$ aliphatic alcohols are selected from the group consisting of octanol, nonanol, decanol, lauryl alcohol and oleyl alcohol.

6. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein Ester compounds between $C_2 \sim C_4$ alkanediols and $C_8 \sim C_{18}$ fatty acids are selected from the group consisting of ethylene glycol monolaurate, propylene glycol monolaurate, propylene glycol dilaurate, and the mixture between propylene glycol monolaurate and propylene glycol dilaurate.

7. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein esters between $C_3 \sim C_4$ alkanetriols and $C_8 \sim C_{18}$ fatty acids are selected from the group consisting of glycerol monooleate, glycerol dioleate, glycerol trioleate, glycerol monolaurate, glycerol dilaurate, glycerol trilaurate, glycerol tricaprilrate, glycerol tricaprate and their mixtures.

8. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein esters between $C_1 \sim C_4$ alcohols and $C_8 \sim C_{18}$ fatty acids are selected from the group consisting of methyl laurate, ethyl oleate and isopropyl myristate.

9. The transdermal delivery composition containing buprenorphine in according to claim 1, wherein terpenes between $C_1 \sim C_4$ alcohols and $C_8 \sim C_{18}$ fatty acids are selected from the group consisting of L-menthol, menthone, D-limonene, 1,8-cineole, nerolidol, carveol and camphor.

10. The patch that contains the transdermal delivery composition containing buprenorphine in according to claim 1.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR99/00778

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC7 A61K 31/485**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimun documentation searched (classification system followed by classification symbols)
IPC6 A61K 31/485, A61K 9/70

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched
Korean Patents and applications for inventions since 1975
Korean Utility models and applications for Utility models since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
WPI, MEDLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | EP 368409 A2 (NORWICH EATON PHARMACEUTICALS, INC.) 16 May 1990 (16. 05. 1990), abstract; page 5, line 11 to page 6, line 4 | 1, 2, 4, 5, 8, 10 |
| Y | US 5601839 A (THERATECH, INC.) 11 February 1997 (11. 02. 1997), abstract; examples 2, 3, 4; claims 12, 13, 15, 19 | 1, 3, 5, 7, 8, 10 |
| Y | US 5069909 A (CYGNUS THERAPEUTIC SYSTEMS) 3 December 1991 (03. 12. 1991), tables 2, 3, 5, 6; examples | 1-8, 10 |
| Y | US 4879297 A (WARNER-LAMBERT COMPANY) 7 November 1989 (07. 11. 1989), examples; claims 1, 2, 4, 10 | 1, 2, 4, 6-8, 10 |
| Y | ROY et al. 'Transdermal delivery of buprenorphine through cadaver skin' In: Journal of Pharmaceutical Sciences, February 1994, Volume 83, Number 2, pages 126-130, see entire document. | 1-8, 10 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
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Information on patent family members

International application No.
PCT/KR99/00778

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|---|---|---|---|
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| | | EP 368409 A3 | 19. 12. 90 |
| | | JP 2-191215 A2 | 27. 07. 90 |
| US 5601839 A | 11. 02. 97 | None | |
| US 5069909 A | 03. 12. 91 | None | |
| US 4879297 A | 07. 11. 89 | None | |